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ORIGINAL ARTICLE

Usefulness of the PERFORM questionnaire to measure fatigue in cancer patients with anemia: a prospective, observational study

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Abstract
Background The PERFORM Questionnaire is a 12-item scale developed for assessing fatigue in cancer patients in the clinical practice. It has advantages over other tools in that it is short and includes beliefs and attitudes of patients about fatigue. It was psychometrically validated in cancer patients with and without anemia.
Purpose We evaluated the usefulness of the PERFORM scale to measure fatigue in a large study focusing exclusively on anemic patients.
Methods This was an observational, multicenter, prospective, 3-month study in cancer patients with hemoglobin (Hb)≤11 g/dl. Fatigue was assessed using the PERFORM questionnaire. The overall score ranges from 12 (no fatigue) to 60 (maximum fatigue).
Results We included 667 patients: 54.1 % women, mean age 60 (standard deviation, 12)years. A highly significant, but mild correlation was observed between low baseline Hb and high patient perception of fatigue (r with PERFORM score=−0.215, $p<0.0001$). Of the patients, 65.8 % improved Hb level during follow-up (increase of ≥1 g/dL and/or achieving >11 g/dL), which translated into a significant improvement in the PERFORM score [mean (95 % confidence interval (CI)] change, −1.2 (−0.04 to −2.4), whereas more fatigue was observed in patients without improvement in Hb [change (95 % CI) in PERFORM, +3.3 (1.5 to 5)]. In a multivariate linear regression analysis, the independent factors associated to fatigue at 3 months were a low Hb level, a low Karnofsky index, active chemotherapy, cancer treatment with palliative intention, and transfusion need in the last 3 months.
Conclusions Minimal increases or decreases in Hb of ≥1 g/dL were associated with meaningful changes in patient-perceived fatigue as measured with the PERFORM questionnaire. In addition to anemia severity, other factors such as active chemotherapy and advanced disease contribute to perception of fatigue by cancer patients.

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Introduction

Fatigue is one of the cancer symptoms with greatest impact in the patients' daily lives, and it is gaining importance as outcome measure [1]. In a recent survey, it was found that 80 % of patients experienced fatigue at least 50 % of the time during treatment, and fatigue was ranked as the symptom most impacting daily life, independently of gender or tumor type [2]. The underlying pathophysiology of cancer-related fatigue is very complex and not completely understood [3]. Although some common mechanisms seem to participate, it is probable that the etiology is not the same in all cancer subpopulations (i.e., patients undergoing active chemotherapy, patients with advanced age, survivors or those with palliative care). It is very important to correctly identify both the biological and psychosocial determinants of fatigue, in order to individualise the therapeutic management.

The etiology of cancer-related fatigue is multifactorial and is related to a variety of factors including chemotherapy with alkylating agents, antimetabolites or platinum compounds, radiotherapy or bone marrow transplantation, changes in blood volume, excess lactate production, hypoglycemia, hypotension, generalized stress responses with or without endocrine dysfunction, sleep disturbances, anxiety, or depression [4–9]. Anemia is one of the factors identified as a causative element in the fatigue experience [10]. Several studies have demonstrated an association between the hemoglobin (Hb) level or its change over time and fatigue intensity assessed by means of Linear Analogue Self-Assessment (LASA) and visual analogue scale (VAS) [11–13]. Furthermore, an association between low hemoglobin and impaired quality of life has also been observed [14].

Anemia is a common complication in cancer patients. According to the European Cancer Anaemia Survey (ECAS), it is present in 72 % of non-solid and 62 % of solid tumor patients [15]. The underlying causes of low Hb levels include chemotherapy with platinum salts, which affect erythropoietin (EPO) production secondarily to nephrotoxicity [16], direct bone marrow damage, caused by almost all cytotoxic drugs [17–19], or also the underlying malignancy itself, which directly decreases erythropoiesis due to an attenuated endogenous EPO response. Chronic anemia of cancer is also characterized by generalized hypoxia, which results in severe fatigue [20].

Other proposed mechanisms of cancer-related fatigue are a dysregulation of the immune function, a dysfunction of the hypothalamic–pituitary–adrenal axis, altered central nervous system serotonin neurotransmitter activity, vagal afferent signaling, and alterations in muscle metabolism [3]. Several findings support these hypotheses. For example, elevated levels of inflammatory cytokines [21], circulating T lymphocytes [22], increased neutrophil counts [23], and blunted cortisol responses [24, 25] have been found to be associated to fatigue in cancer patients. Other studies have identified associations with sleep disturbances [26–28].

The PERFORM questionnaire is a brief, 12-items scale which was developed under the auspice of the Spanish Society of Medical Oncology. In the validation study performed in 437 patients with and without anemia, it demonstrated good psychometric properties (overall Cronbach's alpha and intraclass correlation coefficient of 0.94 and 0.83, respectively; effect size of 0.57 for improved patients and −1 for worsened patients; minimally important difference of 3.5) and accurately reflected improvements in Hb levels [29]. Thus, the PERFORM questionnaire constitutes a good tool to assess perceptions of fatigue of cancer patients in the clinical practice. In order to continue our observations, we have performed a large study focusing exclusively on anemic patients.

The main objective was to prospectively evaluate the association between the Hb level (and its change over time) and self-perceived fatigue and quality of life in cancer patients with anemia, controlling by possible confounding factors (age, gender, tumor type and stage, cancer treatments, presence of comorbidities such as anxiety, depression, malnutrition, sleep disorders, etc.). All these factors were collected, and its effect on fatigue was evaluated simultaneously with the effect of Hb level by means of a multivariate analysis, which allowed the estimation of the independent effects. The secondary objectives were to describe anemia management in the clinical practice of Spanish oncology services and to search other clinical, biochemistry, or sociodemographic factors associated to cancer-related fatigue.

Patients and methods

Study design and population

We performed a prospective, multicenter, observational, 3-month study between September 2007 and July 2008 in medical oncology or palliative care departments of 60 Spanish hospitals. The inclusion criteria were: ambulatory patients ≥18 years of age; with a diagnosis of cancer (any site and length of disease duration); with life expectancy of at least 6 months; and with anemia (symptomatic or asymptomatic) defined as Hb ≤11 g/dl, on inclusion. All eligible subjects who fulfilled the inclusion criteria and provided informed consent were consecutively enrolled in the study. The sample size was calculated based on having 80 % power to detect as significant, at a probability of type I error (alpha) of 0.05, a correlation coefficient of at least 0.1 between longitudinal changes in PERFORM overall score and Hb levels. The calculated number of patients required was 660. The study was approved by the Ethics Committee of the Hospital Clínic in Barcelona and has therefore

been performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

Variables and procedures

Sociodemographic and clinical characteristics, and hematology (hemoglobin, hematocrit, leucocyte, lymphocytes, neutrophils, platelets), biochemistry (sodium, potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, albumin, bilirubin, creatinine, lactate-dehydrogenase (LDH), serum iron, ferritin, transferrin, vitamin B12, folic acid, endogenous EPO), and fatigue measures were collected at baseline visit and 3 months later. Patient perception of fatigue was assessed using the PERFORM questionnaire and two additional instruments, included as control measures: the LASA scale and a VAS.

The PERFORM Questionnaire (Appendix) is a recently developed questionnaire for assessing patient perception on cancer-related fatigue [29, 30]. After the generation of a "pool" of 75 candidate items [31], they were administered to a sample of oncology patients in the preliminary assessment study, conducted between January and September 2005 [30]. The psychometric properties of the final, 12-item version were assessed in the validation study, conducted between November 2005 and September 2006, which showed good feasibility, internal consistency, test–retest reliability, convergent validity, and sensitivity to change [29]. The 12 items, whose responses are on a five-point Likert scale, are distributed in three dimensions "Physical Limitations," "Activities of Daily Living," and "Beliefs and Attitudes." An overall score (range from 12 (no fatigue) to 60 (maximum fatigue)) and three dimension subscores (range from 4 to 20) are obtained, with high scores indicating worse patient perception of cancer-related fatigue.

The LASA scale, previously used for assessing health-related quality of life in cancer patients [12, 32], consists of three items (range for each one from 0 (worse quality of life (QoL)) to 100 (best QoL)): energy scale, activities of daily living, and overall QoL. Each of them identifies a relevant dimension in the evaluation of quality of life in cancer patients. The LASA scale correlates well with Hb levels and has shown good reproducibility and sensitivity to change, with minimally important differences of 9.6 for energy level, 8.7 for activities of daily living, and 9.8 for overall QoL [12]. Finally, each patient self-rated fatigue intensity on a 100-mm horizontal VAS.

Statistical analysis

Correlations between Hb level and patient perception of fatigue at baseline, and between changes in Hb level and changes in fatigue scores during the follow-up were evaluated by using Spearman rank correlation tests. Since the fatigue measures had a normal distribution (confirmed with the Kolmogorov–Smirnov test), changes along time were analyzed using paired *T* tests in the overall sample and in subgroups of patients defined by an improvement or not in their Hb level during the study (increase of ≥1 g/ dL or achieving >11 g/dL). Mean changes and baseline values between subgroups were compared using Mann–Whitney tests or Student's *T* tests (as applicable). The sensitivity to change was assessed by calculating the effect size (i.e., the standardised mean score change) in the subgroups of patients with and without improvement in Hb levels. Changes in hematology and serum biochemistry parameters between baseline and 3-month visits were evaluated using paired *T* tests.

Bivariate associations between patients' characteristics (sociodemographic and clinical variables, hematology and biochemistry values) and fatigue measures were assessed using Student's *T* tests or analysis of variance. Effect measures were expressed as difference in means together with the 95 % confidence interval with respect to the reference category (the one with less fatigue). A multivariate linear regression model was built to identify the independent factors associated to perception of fatigue (overall PERFORM score) at 3 months. Statistical analyses were performed with the SAS® package version 8.2. (SAS Institute, Cary, NC, USA).

Results

Demographic and clinical characteristics

The study included 667 cancer patients with anemia. The main characteristics of the study population are shown in Table 1.

Hematology and serum biochemistry parameters where mostly within normal limits (Table 2), both at baseline and 3-month visit, with the exception of: low hematocrit and Hb levels (as defined by protocol), and elevated mean LDH and endogenous EPO levels. Ferritin levels were in the upper limit of normality. During the prospective follow-up, the Hb ($p<0.001$), hematocrit ($p<0.001$), serum iron ($p=0.026$), AST ($p=0.002$), and albumin levels ($p<0.001$) displayed a significant increase, whereas the platelet count ($p<0.001$) and the glucose levels ($p=0.007$) decreased (Table 2).

Evolution and management of anemia

At baseline, 65.1, 33.3, and 1.6 % of patients had mild (>10 to ≤11 g/dL), moderate (≥8 to ≤10 g/dL), and severe anemia (<8 g/dL), respectively (Table 3). At 3 months, the percentage of anemic patients had decreased to 43.3 %, and 65.8 % of patients had an improvement in their Hb level (defined as increase of ≥1 g/dL or achieving >11 g/dL). The severity of anemia in the subgroup of patients who remained with Hb <11 g/dL was similar than at baseline (Table 3).

Table 1 Demographic and clinical characteristics of the study population at baseline and 3-month visits (*N*=667)

	Valid *N*[a]	Baseline visit	Valid *N*[a]	3-month visit
Gender, *N* (%)	667			
Men		306 (45.9)		–
Women		361 (54.1)		–
Age (years)	667			
Mean (SD)		59.9 (12.1)		–
Range		[20–89]		–
Cancer type[b], *N* (%)	667			
Breast		129 (19.3)		–
Lung		133 (19.9)		–
Ovarian		52 (7.8)		–
Head and neck		33 (5.0)		–
Genitourinary		49 (7.3)		–
Gastrointestinal		194 (29.1)		–
Lymphoma		16 (2.4)		–
Other		117 (17.5)		–
Time since diagnosis (years)	657			
Mean (SD)		2.1 (3.1)		–
Range		[0–27.4]		–
Family situation, *N* (%)	665			
Patient does not need care from another person		450 (67.7)		–
Patient needs and receives care from a relative, a caregiver or both		215 (32.3)		–
Spread of cancer, *N* (%)	666		537	
Local		123 (18.5)		113 (21.0)
Locoregional		163 (24.4)		111 (20.7)
Metastatic		380 (57.1)		313 (58.3)
Karnofsky index (%)	651			
Mean (SD)		81.8 (12.1)		–
Range		[1–100]		–
Cancer treatment, *N* (%)	667		541	
Without treatment		62 (9.3)		176 (32.5)
In treatment[b]		605 (90.7)		365 (67.5)
Chemotherapy		553 (82.9)		220 (40.7)
Monoclonal antibodies		43 (6.4)		35 (6.5)
Radiotherapy		48 (7.2)		23 (4.3)
Hormone therapy		20 (3.0)		28 (5.2)
Interferon		1 (0.1)		1 (0.2)
Symptomatic treatment		70 (10.5)		54 (10.0)
Pain		51 (7.6)		36 (6.7)
Other		28 (4.2)		34 (6.3)
Treatment intention	602		365	
Adjuvant		111 (18.4)		57 (15.6)
Curative		83 (13.8)		38 (10.4)
Palliative		408 (67.8)		270 (74.0)
Comorbidities[b]	667			
Anxiety		75 (11.2)		62 (11.5)
Depression		65 (9.7)		58 (10.7)
Dehydration		4 (0.6)		4 (0.7)
Infection		8 (1.2)		7 (1.3)
Heart failure		10 (1.5)		13 (2.4)
Respiratory failure		42 (6.3)		32 (5.9)
Chronic kidney disease		14 (2.1)		10 (1.8)
Liver disease		14 (2.1)		13 (2.4)
Malnutrition		12 (1.8)		25 (4.6)
Diarrhoea		5 (0.75)		2 (0.4)
Sleep disorders		24 (3.6)		17 (3.1)

SD standard deviation

[a] There were missing values in the data set

[b] Each patient could have more than one response

Only 42.4 % of patients received treatment for anemia at baseline visit, mainly erythropoiesis-stimulating agents (ESAs) and/or supplements (87 % iron supplementation; Table 3). At 3-month visit, the percentage of patients with treatment for anemia had increased to 55.8 % ($p<0.001$), but the relative distribution of the different treatments was similar (Table 3).

Patients treated with transfusions alone or in combination had lower mean baseline Hb level (9.1 (standard deviation (SD), 1.0) g/dL) than any other group (10.0 (SD, 0.7) g/dL in patients with ESA alone, 9.8 (SD, 0.7) g/dL in patients with ESA and supplements, 10.2 (SD, 0.7) g/dL in patients with supplements alone, and 10.3 (SD, 0.6) g/dL in patients without treatment, $p<0.0001$ between groups). Mean change in Hb during the follow-up was similar in all these subgroups ($p=0.511$, data not shown).

Fatigue measures and correlation with Hb

Table 3 displays mean fatigue scores at baseline and 3-month visits in the overall group for the three administered instruments. At baseline, both the PERFORM questionnaire and the two control measures (LASA and VAS) reflected an impairment of medium-degree intensity. Mean PERFORM overall score at baseline in patients with mild, moderate, and severe anemia was 31.6 (SD, 12.5), 36.6 (SD, 13.9), and 41.6 (SD, 11.9), respectively.

At 3 months, a significant improvement in fatigue was observed as measured by the "Beliefs and attitudes" dimension of the PERFORM questionnaire ($p=0.036$) and by the three LASA subcales ($p=0.006$, 0.003, and 0.004, respectively; Table 3).

Table 2 Hematology and serum biochemistry parameters in the study population at baseline and 3-month visits

	Baseline visit		3-month visit		*P* value
	Valid *N*[a]	Mean (SD)	Valid *N*[a]	Mean (SD)	
Hemoglobin (g/dL)	667	10.1 (0.8)	527	11.2 (1.5)	<0.001
Hematocrit (%)	650	30.5 (2.7)	519	33.6 (4.5)	<0.001
Leucocyte (10^3/mm^3)	654	6.3 (3.6)	522	6.3 (3.4)	0.666
Lymphocytes (10^3/mm^3)	386	1.4 (0.7)	280	1.4 (0.7)	0.706
Neutrophils (10^3/mm^3)	389	3.9 (2.5)	278	3.8 (2.1)	0.716
Platelets (10^3/mm^3)	637	282.2 (133.2)	519	247.7 (111)	<0.001
Sodium (mEq/L)	474	139.2 (3.2)	414	139.5 (3.4)	0.133
Potassium (mEq/L)	466	4.3 (0.5)	403	4.3 (0.5)	0.326
AST (U/L)	395	25.9 (23.8)	348	32.5 (31.8)	0.002
ALT (U/L)	408	28.2 (22.9)	356	29.5 (22.7)	0.243
Glucose (mmol/L)	486	5.9 (1.9)	421	5.7 (1.7)	0.007
Albumin (g/dL)	254	3.8 (0.6)	250	3.9 (0.6)	<0.001
Bilirubin (mg/dL)	410	0.5 (0.4)	357	0.6 (0.3)	0.164
Creatinine (mg/dL)	550	0.9 (0.4)	470	0.9 (0.4)	0.380
LDH (U/L)	300	424.8 (242.9)	276	404.3 (222)	0.329
Serum iron (μg/dL)	78	51.2 (33.5)	71	58.9 (28.5)	0.026
Ferritin (ng/dL)	48	300.3 (316.4)	49	275.8 (291.2)	0.652
Transferrin (%)	37	18 (7.5)	41	17.8 (8.8)	0.837
Vitamin B12 (pg/mL)	40	582.9 (501.4)	45	592.1 (400.1)	0.400
Folic acid (ng/mL)	39	9.2 (6)	34	10.3 (6.2)	0.518
Endogenous EPO (IU/L)	4	56.7 (39.9)	7	50.8 (30.5)	0.777

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *EPO* epoetin, *LDH* lactate-dehydrogenase

[a]There were missing values in the data set

At baseline, the correlations between fatigue measures and Hb level were statistically significant in all cases, and showed relationships of moderate degree (r=−0.215, −0.187, −0.221, −0.164, p<0.001 in all cases, for the PERFORM overall, activities of daily living, beliefs and attitudes, and physical limitations scores; r=−0.134, p<0.001 for the VAS score; and r=0.108, p=0.005, r=0.099, p=0.01 and r=0.103, p=0.007 for the energy, activities of daily living, and overall QoL LASA subscales, respectively; Table 4).

At 3 months, the correlation coefficient between Hb level and PERFORM overall score was similar than at baseline visit (r=−0.249, p<0.0001). A significant negative correlation was also observed between 3-month changes in Hb level and 3-month changes in PERFORM score (r=−0.255, p<0.0001).

Fatigue in subgroups with and without improvement in Hb

Table 5 shows 3-month changes in fatigue scores in patients with and without improvement in Hb level. At baseline, no significant differences were observed between these two groups.

During the follow-up, mean changes in fatigue scores were significantly different for the three questionnaires, resulting in effect sizes ranging from 0.07 to 0.20 (absolute values) in improved patients, and from 0.12 to 0.32 in non-improved patients (Table 5).

Factors associated to fatigue

At baseline visit, factors associated to fatigue as measured by overall PERFORM score were: Hb level (r=−0.215, p<0.0001), low Karnofsky score (r=−0.275, p<0.0001), high ferritin levels (r=0.338, p=0.040), need for caregiver (difference in mean versus patients who do not need care, +8.7, p<0.0001), treatment with palliative intention (+5.2 versus treatment with curative intention, p=0.001), and metastatic tumor (+4.3 versus local tumor, p=0.018). No relationship was found with age, gender, educational level, serum iron, transferrin saturation, time since diagnosis, tumor location or active cancer treatment (data not shown).

At 3 months, factors associated to fatigue were: longer time since diagnosis, lower Karnofsky index, lower Hb at baseline and at 3 months, lower change in Hb during the follow-up, lower serum iron at baseline, lung cancer type, metastatic tumor, active cancer treatment, chemotherapy administration, palliative cancer treatment intention, heart and/or respiratory failure, administration of ESA, and transfusion use (Table 6).

After multivariate adjustment, the independent factors that remained associated to fatigue (global PERFORM score) at 3 months were: a low Hb level (coefficient β +1.43 (+0.60 to +2.26) for each −1 g/dL, p=0.001), a low Karnofsky index

Table 3 Description of anemia degree, treatments for anemia, and patient-perception of fatigue in the study population at baseline and 3-month visits

	Valid *N*[a]	Baseline visit	Valid *N*[a]	3-month visit	*P* value
Anemia degree (g/dL)	667		527		<0.001
No anemia (>11 g/dL)		0		299 (56.7)	
Mild anemia (>10 to ≤11 g/dL)		434 (65.1)		128 (24.3)	
Moderate anemia (≥8 to ≤10 g/dL)		222 (33.3)		87 (16.5)	
Severe anemia (<8 g/dL)		11 (1.6)		13 (2.5)	
Type of treatment for anemia, *N* (%)	667		541		<0.001
None		384 (57.6)		239 (44.2)	
Only transfusions		32 (4.8)		36 (6.6)	
Only supplements		69 (10.3)		67 (12.4)	
Only ESA		90 (13.5)		80 (14.8)	
Transfusions+supplements		12 (1.8)		11 (2)	
Transfusion+ESA		20 (3)		29 (5.4)	
ESA+supplements		47 (7)		56 (10.3)	
Transfusion+ESA+supplements		13 (1.9)		23 (4.3)	
PERFORM questionnaire, mean (SD)					
Global score	542	33.4 (13.2)	427	31.9 (13.3)	0.051
Activities of daily living	618	11.1 (4.3)	483	10.7 (4.4)	0.140
Beliefs and attitudes	584	11.4 (4.7)	461	10.8 (4.7)	0.036
Physical limitations	633	11.0 (5.0)	500	10.5 (5.0)	0.106
VAS fatigue (mm), mean (SD)	652	45.5 (27.6)	510	46.4 (28.8)	0.597
LASA (mm), mean (SD)					
Energy	656	52.3 (23.7)	512	56.0 (24.5)	0.006
Activities of daily living	652	53.6 (27.2)	512	58.1 (26.6)	0.003
Overall quality of life	656	56.1 (23.7)	514	59.7 (24.5)	0.004

Each patient could have more than one response; supplements include: iron, B12 vitamin, folic acid

ESA erythropoiesis-stimulating agents, *LASA* Linear Analogue Self-Assessment, *SD* standard deviation, *VAS* Visual Analogue Scale

[a] There were missing values in the data set

Table 4 Correlation between hemoglobin level and patient-perception of fatigue at baseline visit (*N*=667)

Baseline fatigue evaluations	Baseline hemoglobin level		
	N[a]	Correlation coefficient[b]	*P* value
PERFORM questionnaire			
Global score	542	−0.215	<0.001
Activities of daily living	618	−0.187	<0.001
Beliefs and attitudes	584	−0.221	<0.001
Physical limitations	633	−0.164	<0.001
VAS fatigue	652	−0.134	<0.001
LASA			
Energy	656	0.108	0.005
Activities of daily living	652	0.099	0.010
Overall quality of life	656	0.103	0.007

LASA Linear Analogue Self-Assessment, *VAS* Visual Analogue Scale

[a] There were missing values in the data set

[b] Rho Spearman

(coefficient β +0.19 (+0.08 to +0.29) for each +1 %, $p<0.0001$), active chemotherapy (coefficient β 5.07 (+1.81 to +8.32), $p=0.002$), cancer treatment with palliative intention (coefficient β +2.97 (+0.33 to +5.61), $p=0.028$), and transfusion need in the last 3 months (coefficient β +4.66 (+0.34 to +8.98), $p=0.035$).

Discussion

The PERFORM questionnaire is a brief, recently validated scale, specifically developed in the Spanish cultural environment, for the assessment of perceptions and beliefs about cancer-related fatigue, which has demonstrated excellent psychometric properties [30]. The present study constitutes the first use of this 12-item tool in the routine management of Spanish cancer patients.

At baseline, we administered the PERFORM questionnaire to a cohort characterized by low Hb levels, with the aim to describe the relationship between anemia and perception of fatigue by patients. The significant correlation found between

Table 5 Change in patient-perception of fatigue between baseline and 3-month visit in subgroups of patients with or without improvement in hemoglobin levels (defined as an increase ≥1 g/dL or achieving >11 g/dL)

	Patients without improvement in Hb (*N*=180)				Patients with improvement in Hb (*N*=347)				*P* value[b]
	Baseline visit	3-month visit	Mean change (95 % CI)	Effect size	Baseline visit[a]	3-month visit	Mean change (95 % CI)	Effect size	
PERFORM questionnaire, mean									
Global score	32.7	35.6	3.3 (1.6 to 5)*	0.22	31.4	29.9	−1.2 (−0.04 to −2.4)*	−0.12	<0.001
Activities of daily living	10.8	11.9	0.95 (0.4 to 1.5)*	0.26	10.6	10.0	−0.59 (−0.1 to −1.0)*	−0.14	<0.001
Beliefs and attitudes	11.2	11.9	0.86 (0.2 to 1.5)*	0.14	10.8	10.2	−0.36 (−0.8 to 0.1)	−0.14	0.004
Physical limitations	10.9	11.9	1.2 (0.5 to 1.9)*	0.19	10.1	9.8	−0.33 (−0.8 to 0.1)	−0.07	<0.001
VAS fatigue, mean, mm	44.9	53.7	9.2 (5.2 to 13.2)*	0.32	42.3	42.4	0.60 (−2.3 to 3.5)	0.01	<0.001
LASA, mean, mm									
Energy	53.1	50.4	−2.6 (−6.6 to 1.4)	−0.12	55.1	59.3	4.2 (1.5 to 6.9)*	0.18	0.003
Activities of daily living	55.9	52.5	−3.7 (−8.0 to 0.6)	−0.13	56.1	61.2	4.8 (1.8 to 7.8)*	0.19	0.001
Overall quality of life	57.5	52.4	−5.5 (−9.3 to −1.7)*	−0.23	59.2	63.8	4.5 (2.1 to 6.9)*	0.20	<0.001

In the PERFORM questionnaire and VAS-fatigue low scores indicate less impact of fatigue on the patient's life; in the LASA questionnaire, low scores indicate worse quality of life

CI confidence interval, *Hb* hemoglobin, *LASA* Linear Analogue Self-Assessment, *VAS* Visual Analogue Scale

*$p<0.05$ between baseline and 3-month visit (within-subgroup paired analysis)

[a] No significant differences were found in baseline measures of fatigue between the two subgroups

[b] Comparison of mean change between the two subgroups

Table 6 Association between clinical and sociodemographic characteristics of cancer patients and perception of fatigue at 3-month visit (PERFORM questionnaire, overall score)

	PERFORM score at 3 months	
Continuous variables	Coefficient of correlation	*P* value
Time since diagnosis	0.099	0.042
Karnofsky index	−0.199	<0.0001
Hemoglobin at baseline	−0.115	0.017
Hemoglobin at 3 months	−0.249	<0.0001
Change in hemoglobin	−0.196	<0.0001
Serum iron at baseline	−0.307	0.048
Categorical variables	Difference in mean PERFORM score (95 % CI)	*P* value
Cancer type		0.012
Lung	+4.5 (+7.9 to +1.0)	
Other	Reference	
Spread of cancer, *N* (%)		0.002
Local	Reference	
Locoregional	+0.9 (−2.6 to +4.3)	
Metastatic	+5.4 (+2.2 to +8.5)	
Cancer treatment		0.002
Without treatment	Reference	
In treatment	+7.0 (+3.8 to +10.2)	
Type of cancer treatment		<0.0001
Chemotherapy	+5.9 (+3.0 to +8.8)	
Without chemotherapy	Reference	
Cancer treatment intention		<0.0001
Palliative	+6.3 (+3.9 to +8.7)	
Adjuvant or curative	Reference	
Comorbidities		0.030
Heart and/or respiratory failure	+5.3 (+0.6 to +10.0)	
Without heart and/or respiratory failure	Reference	
Type of treatment for anemia		0.006
Transfusions	+6.3 (+2.0 to +10.7)	
Without transfusions	Reference	
Type of treatment for anemia		0.001
ESA	+5.0 (+2.1 to +7.9)	
Without ESA	Reference	

No significant association was observed between overall PERFORM score and the following variables: age, gender, ferritin levels, transferrin saturation, radiotherapy, hormone therapy, monoclonal antibodies, interferon, symptomatic treatment, supplements, chronic kidney disease, anxiety and/or depression, dehydration and/or malnutrition and/or diarrhea, infection, liver disease, sleep disorders

CI confidence interval, *ESA* erythropoiesis-stimulating agent

the Hb level and the three fatigue measures (the PERFORM questionnaire and the two control measures LASA and VAS), ranging between 0.10 and 0.22, is in line with what has been published so far in the literature [12]. During the follow-up, approximately 50 % of patients had their anemia corrected, and the PERFORM questionnaire was able to capture an improvement in fatigue perception, whereas the LASA scale did not show a significant change. In patients without Hb improvement, an overall worsening of fatigue and QoL was observed, suggesting that patient's overall status had deteriorated due to cancer progression. In the multivariate analysis, a decrease in Hb levels as little as 1 g/dL was independently associated to a worsening of fatigue perception, after controlling by demographic and clinical characteristics, cancer and anemia treatments, and other biochemistry values. Thus, our results suggest that 1 g/dL is a noteworthy change for the patient's point of view, at least in anemic patients. In a study with patients in palliative care, differences in fatigue were observed only between subgroups defined by a cutoff level of 10 g/dL, but not when the cutoff level was set to 12 g/dL [33]. We noticed a similar degree of correlation between fatigue and absolute Hb levels at baseline and at 3 months, after anemia correction, which suggests that further benefits can be observed in patient-reported fatigue at levels above 11 g/dl. A previous study of anemia correction with epoetin alfa reported that the greatest QoL increase was recorded when patients approached an Hb level of 12 g/dL, independent of the baseline Hb level [13].

Regarding the management of anemia in the study sample, it is similar than that described in previous studies [15], although we found a slightly higher use of iron supplementation than in

the ECAS. Besides Hb level, other factors associated to fatigue in our cohort were the presence of advanced disease (as indicated by the significance of the variable "palliative cancer treatment intention"), chemotherapy administration, and a low Karnofsky index. The relationship found with transfusion need could be explained by the fact that transfusions have only transient effects, and have a limited capacity to ameliorate the symptoms of anemia [34, 35].

We found no significant relationship between fatigue and age, as previously described [36]. Gerber et al. [14], in a cohort of breast cancer patients, found that the biological characteristics associated with fatigue were high body mass index and white blood cell counts. Other studies in breast and liver cancer [37, 38] and in patients with palliative care [33] found that fatigue was associated to psychological factors such as distress, depression, or anxiety (less prevalent in our sample). Through the results of the present and other recent studies, it is becoming evident that cancer-related fatigue has several causal mechanisms [14]. For this reason, an individualised approach to its therapeutic management is needed [39–46].

The present study supports the potential usefulness of the brief PERFORM questionnaire for quickly assessing patient perception of fatigue in the clinical practice. A systematic review conducted in 2009 identified an extremely high number (up to 40) of validated instruments for measuring fatigue in cancer patients [47]. Only few of them were optimally tested for validity and reliability [48], and most tools were relatively insensitive to differences in fatigue to cancer stage. In addition, most instruments were too long to be administered in patients with advanced cancer. In the present study, the PERFORM questionnaire, which is almost as short as the nine-item Brief Fatigue Inventory, has demonstrated good sensitivity to change, and has the advantage over other tools that includes beliefs and attitudes of patients about fatigue. It is possible that this newly added dimension explains our findings about factors predicting fatigue not found in any previous study (i.e., transfusion need).

The main limitation of the study is the observational design, which does not allow the establishment of causal relationships. Treatment bias does not allow comparing outcomes in Hb or fatigue between subgroups defined by therapeutic management of anemia. Indirect associations between unmeasured variables and some of the described factors predicting fatigue might account for some of our findings, and thus results must be interpreted with caution.

Conclusions

Minimal increases or decreases in Hb of ≥1 g/dL were associated with meaningful changes in patient-perceived fatigue as measured with the brief, 12-item PERFORM questionnaire. In addition to anemia severity, other factors such as active chemotherapy and advanced disease contribute to perceptions of fatigue by cancer patients. These results represent new evidence of the potential usefulness of PERFORM questionnaire for monitoring symptoms of fatigue in cancer patients.

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Appendix

Table 7 PERFORM questionnaire

In the last 2 weeks, how frequent have you felt like these items?	Never	Sometimes	Often	Usually	Always
1. The slightest effort makes me very tired.	1	2	3	4	5
2. My tiredness (due to my illness or its treatment) has been very different to "normal" tiredness.	1	2	3	4	5
3. I've been tired the whole day long	1	2	3	4	5
4. I've spent the whole day sitting down because of my tiredness.	1	2	3	4	5
5. When I was tired, I've had to interrupt what I was doing and rest so as to be able to continue.	1	2	3	4	5
6. I've been very slow performing my usual activities.	1	2	3	4	5
7. I've needed help with tasks around the house because of my tiredness	1	2	3	4	5
8. I've felt bad about feeling tired at work.	1	2	3	4	5
9. In general, I believe my tiredness has made my life worse.	1	2	3	4	5
10. I've felt that I'm going downhill because of my tiredness.	1	2	3	4	5
11. I feel my tiredness has prevented me from living a normal life.	1	2	3	4	5
12. I've stopped doing things I liked doing because of my tiredness.	1	2	3	4	5

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